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# LETTER TO THE EDITOR

# Re: Twenty-Year Follow-Up in Patients with Aplastic Anemia Given Marrow Grafts from HLA-Identical Siblings and Randomized to Receive Methotrexate/Cyclosporine or Methotrexate Alone for Prevention of Graft-versus-Host Disease

From December 1981 to March 1985, 46 patients with severe aplastic anemia were enrolled in a prospective randomized trial analyzing the safety and efficacy of methotrexate/cyclosporine (n = 22) versus methotrexate alone (n = 24) for prevention of acute graft-versus-host disease (GVHD) after marrow transplantation from HLA-identical siblings [1]. Fewer methotrexate/cyclosporine-treated patients had grade II to IV acute GVHD (18%) compared with methotrexate-treated patients (54%; $P = .01$). In addition, no patient given methotrexate/cyclosporine experienced grade III or IV acute GVHD, compared with 3 and 6 patients, respectively, given methotrexate alone. The reduction in acute GVHD was accompanied by a trend for improved early survival [1,2]. The current update with follow-up ranging from 18 to 23 years shows that the survival advantage suggested by early follow-up has persisted. Seventy-three percent of the methotrexate/cyclosporine-treated patients are alive, compared with 42% of the methotrexate-treated patients ($P = .06$; Figure 1A).

Patients were conditioned with cyclophosphamide 200 mg/kg body weight intravenously and were then given marrow grafts from HLA-identical siblings. Postgrafting immunosuppression was either methotrexate on days 1, 3, 6, and 11 combined with cyclosporine for 6 months or methotrexate alone given on days 1, 3, 6, and 11 and then once weekly until day 102. Details on patient characteristics, stratification for risk factors, and the random assignment of postgrafting immunosuppression were described in the original article [1].

Three patients, 2 given methotrexate/cyclosporine and 1 given methotrexate, rejected their grafts (n = 2) or experienced graft failure (n = 1). The 2 methotrexate/cyclosporine-treated patients were successfully given second transplants from the original marrow donors 7 and 20 months after their first transplantations, and they are alive with Karnofsky scores of 100, whereas the methotrexate-treated patient died, after a second transplantation, from sepsis and complications associated with chronic GVHD.

The prevalence curves [3] describing the onset of chronic GVHD and its resolution in response to therapy were comparable for the 2 study arms ($P = .40$; Figure 1B). None of the methotrexate/cyclosporine-treated patients and 1 methotrexate-treated patient currently continue on immunosuppression. Twelve of 16 surviving methotrexate/cyclosporine-treated patients have Karnofsky performance scores of 100, and 4 have scores of 90. All 10 surviving methotrexate-treated patients have scores of 100. Eighteen of 26 surviving patients are completely healthy; 4 patients are hepatitis C virus positive (this virus was presumably acquired through preceding transfusions); 1 of the 4 recently developed diabetes mellitus; 1 has lumbosacral osteoarthritis and hypertension; 1 patient has hypertension; and 1 patient had squamous cell carcinoma of the skin that was surgically removed. Five methotrexate/cyclosporine-treated patients died. Three died from GVHD-related complications, including hepatic encephalopathy (day 199), sepsis (day 920), and bronchoalveolitis (day 950), and 2 patients died early, 1 from massive brain hemorrhage (day 12) and 1 from pulmonary and renal failure (day 3). Fourteen methotrexate-treated patients died. Six died from GVHD-associated complications, including disseminated aspergillosis and cytomegalovirus (CMV) disease (day 64), interstitial pneumonitis and CMV of the gut (day 103), pneumonia and cerebral infarcts (day 108), sepsis (day 216), fulminant hepatic failure (day 338), and septic shock (day 726). Two methotrexate-treated patients died from multiorgan failure secondary to sepsis (days 25 and 192), 1 from interstitial and CMV pneumonia (day 35), 1 from graft failure and sepsis (day 393), 1 from suicide (day 1123), 1 from human immunodeficiency virus–related causes (day

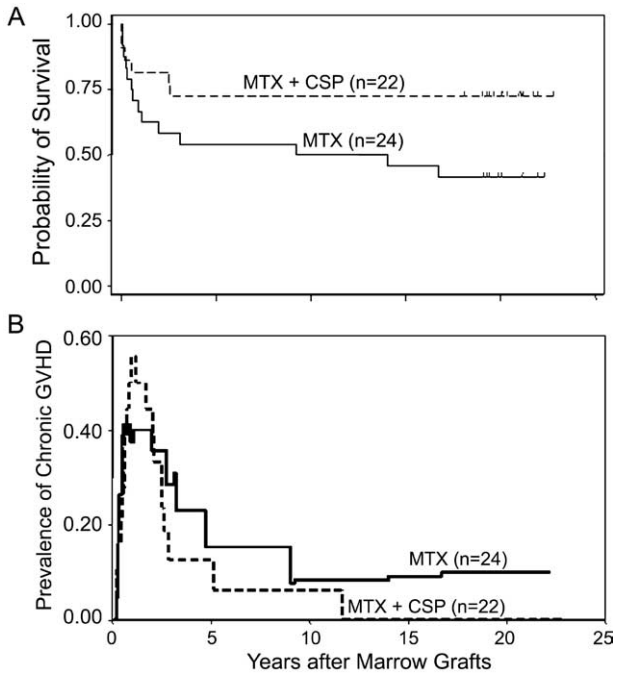


**Figure 1.** A, Kaplan-Meier product estimates for overall survival. B, Prevalence [3] of chronic GVHD among patients with aplastic anemia who were administered marrow grafts from HLA-identical siblings with either methotrexate/cyclosporine (MTX + CSP) or methotrexate alone (MTX) for GVHD prophylaxis.

3380), 1 from sudden cardiac death (day 5123), and 1 from cancer of the jaw (day 6111).

We concluded that patients with aplastic anemia given HLA-identical marrow grafts and treated with methotrexate/cyclosporine had both a significantly decreased incidence and severity of acute GVHD; this resulted in a decrease in early transplant-related mortality compared with patients given methotrexate alone. The early survival advantage has persisted. The methotrexate/cyclosporine combination did not reduce the incidence of chronic GVHD. With observation times ranging from 18 to 23 years, all methotrexate/cyclosporine-teated patients who developed chronic GVHD have shown resolution of their disease, and immunosuppressive therapy has been discontinued.

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## REFERENCES

1. Storb R, Deeg HJ, Farewell V, et al. Marrow transplantation for severe aplastic anemia: methotrexate alone compared with a combination of methotrexate and cyclosporine for prevention of acute graft-versus-host disease. *Blood*. 1986;68:119-125.
2. Storb R, Deeg HJ, Pepe M, et al. Graft-versus-host disease prevention by methotrexate combined with cyclosporin compared to methotrexate alone in patients given marrow grafts for severe aplastic anaemia: long-term follow-up of a controlled trial. *Br J Haematol*. 1989;72:567-572.
3. Pepe MS, Longton G, Pettinger M, Mori M, Fisher LD, Storb R. Summarizing data on survival, relapse, and chronic graft-versus-host disease after bone marrow transplantation: motivation for and description of new methods. *Br J Haematol*. 1993; 83:602-607.

*Mohamed L. Sorror, MD*[1]
*Wendy Leisenring, ScD*[1,2]
*H. Joachim Deeg, MD*[1,3]
*Paul J. Martin, MD*[1,3]
*Rainer Storb, MD*[1,3]
[1]*Fred Hutchinson Cancer Research Center*
[2]*School of Public Health*
[3]*University of Washington School of Medicine*
*Seattle, WA*